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The Work of Paul Ehrlich and His Position in the History of Medical Research

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It requires no great effort of imagination to picture the state of medicine at the time of *Ehrlich*'s death in 1915 but to transport the mind back to the period of his birth and to picture the primitive state of medical science in 1854 requires a very conscious effort. That effort is in part a measure of the great contribution made by *Paul Ehrlich* to medical science.

Throughout the middle ages disease had been regarded as an unfortunate manifestation of divine justice; true, this theocratic view had been replaced during the renaissance by the idea that disease was a natural phenomenon brought about by the inhalation of bad airs or by changes in the weather but as late as 1857, three years after *Ehrlich*'s birth, we find that Sir *Thomas Watson*, a leading teacher of the period, could say in his Lectures on the Principles and Practice of Medicine: "great differences of opinion still exist in respect to the contagious quality of certain forms of puerperal peritonitis just as great differences exist as to the contagiousness of continued fevers of cholera and plague. There are persons who regard the whole notion of contagion as a mere bugbear." And these persons were not cranks but members, indeed possibly a majority of the members of the medical profession.

This refusal to accept the contagious theory of disease is a curious example of conditioned thinking. The medical profession had for hundreds of years been conditioned to a certain traditional mode of thought so that they were less prepared to accept novel ideas than the layman with an unprejudiced mind. Thus *Boccaccio* in 1348 makes reference to the danger of walking with the sick or handling their clothes. Yet, when *Semmelweis* was appointed to the first obstretric ward of the Allgemeines Krankenhaus in Vienna in 1846 he found that the mortality rate from puerperal sepsis was so high that women begged in tears not to be taken into the ward. He found that students were coming straight to the ward from post mortem dissections without washing their hands yet, when he instituted a system of hand washing in dilute calcium hypochlorite and reduced the mortality rate his ideas on contagion were ridiculed by his colleagues and he quitted Vienna in disgust.

In 1546 there was published in Venice a small book by *Girolamo Fracastoro* in which there was a complete outline of the contagious theory of disease, but *Fracastoro* lacked a microscope and his ideas died with him. One hundred and fifty years later, *Antony van Leeuwenhoek*, using his improved microscopes was sending accurate descriptions of intestinal bacteria to the Royal Society in London but he knew nothing of disease. *Dobell* (1932) in his classical biography says "neither here nor elsewhere in his writings does *Leeuwenhoek* associate the entozoic protozoa or bacteria with the causation of disease". One hundred years after the death of *Leeuwenhoek* there was still no marriage between the two ideas but in 1834 another amateur, an Italian lawyer *Agostino Bassi*, set light to the accumulated pile of ignorance and observation by his demonstration that the silk worm disease "mal del segno" was transmitted from worm to worm by a cryptogamic fungus. At first the pile was slow to burn but fanned by the efforts of *Pasteur*, *Lister*, *Davaine* and *Koch* it finally burst into flame just as *Paul Ehrlich* completed his medical course. In 1878 *Robert Koch* published his studies on infective diseases in which he proved by experiments on animals that a series of clinically distinct diseases could be produced by the injection of putrid material and could be maintained by serial passage. In the same year *Ehrlich* presented his doctorate thesis "Beiträge zur Theorie und Praxis der histologischen Färbung" (his first publication was on the same subject and appeared one year earlier).

The Guiding Principle

Ehrlich's work can be divided into three main periods. From 1877–1890 he developed the theme outlined in his doctorate thesis, from 1891 to 1904 his interest was mainly centered on immunity and from 1905 onwards on chemotherapy while throughout the whole period he maintained an active interest in cancer. Despite the wide field thus covered, a single thread of thought runs through his entire life work. It is best expressed in his own words. "I have been more and more forcibly impressed with the idea that in a study of the fundamental biological phenomena, the significance of morphological structure is far less than the significance of the chemistry involved. It is obvious that in order to effect a given chemical process certain mechanical conditions must be fulfilled. In other words the production of any chemical action necessitates the presence and the suitable arrangement of apparatus. The essential feature, however, is neither apparatus nor form, but the constituents involved; for without changing the apparatus hundreds of different combinations can be effected according to the components employed. Similarly in biology I believe that the morphological arrangement of the organs and cells is not the essential feature but that this is rather to be sought for in chemical differences of the constituents".

It was a fortunate chance that *Ehrlich*'s cousin and close friend *Carl Weigert* was particularly interested in the new aniline dyes so that during the formative period of *Ehrlich*'s medical education he was introduced to the chemistry of these dyes and advised to study under *Cohnheim* and *Heidenhain*. Here he had to learn for his "Physikum" a considerable amount of chemistry and as a result became both interested and proficient in the subject. *Ehrlich*'s own comment on this training was "I really believe that my talents lie in the field of chemistry; I can picture the chemical formulæ in my mental vision and I believe that this fact has been of the greatest value to me in my studies". It was this capacity for visualization of chemical events which was to be of such value to *Ehrlich* in his formulation of theories as to the mode of action of dyes, drugs and toxins.

First Period: Researches on Dyes

In his first three papers (1877–1879) *Ehrlich* made a systematic study of the staining properties of aniline dyes. He was the first to recognize that dyes fall into two groups, acidic and basic which are distinct both chemically and histologically. He showed the difference between acidophile and basophile leucocytes and showed that structures which could not be stained with either acidic or basic dyes could be stained with "neutral" stains such as rosaniline picrate. Three years later in 1882 he introduced the principle of adding aniline water to basic dyes and thus laid the foundation for the universally applied Gram stain. *Ehrlich*'s interest in methylene blue also dates from this period. It led almost at once to the development of a practical method for staining the tubercle bacillus and ultimately to the development of synthetic antimalarials.

Receptors

Ehrlich's researches on stains had as their objective not so much the development of new histological methods, though these were supplied, as the throwing of light on the larger question of the combining affinities of the tissues and the *intra vitam* distribution of drugs. "*Das Sauerstoffbedürfnis des Organismus*" published as a small book in 1885 contains an account of experiments designed to measure the affinity of tissues for oxygen. Two dyes were employed, alizarin blue and indophenol, both of which are reducible to leuco compounds, one more readily than the other. Each dye was introduced into the circulation of a living animal which was killed some time later. *Ehrlich* found that some organs were coloured blue while others had reduced the dye to the colourless leuco-product. Some organs which did not ordinarily reduce the dye did so when a state of asphyxia was established. In this way he was able to deduce the relative affinities of different tissues for oxygen.

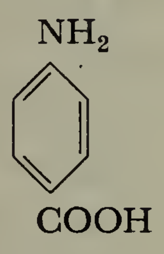
This book is more important however than as a record of a series of highly original experiments, for it contains *Ehrlich*'s ideas and shows his essentially biochemical approach to the problems of cell respiration, cell metabolism and pharmacological action. In studying the specificity of stains for fixed cell preparations and the distribution of dyes when injected into the living animal Ehrlich was impressed by the importance of drug distribution in therapeutics but unlike the majority of his contemporaries he was not satisfied with such vague terms as "colloidal adsorption" and constantly sought for a structural basis for pharmacological specificity. In his own words "chemical substances are only able to exercise an action on the tissue elements with which they are able to establish an intimate chemical relationship". In 1885 a few proteins had been isolated and a few enzymes examined but there was at this time no conception of the part played either by proteins or by enzymes in cellular economy so that *Ehrlich* was forced to discuss his pharmacological problems using a terminology which appears archaic to the modern eye. His cells contained "protoplasm" looked upon as a sort of giant molecule characteristic of all living material. It was clear to *Ehrlich* however that protoplasm was not a uniform material but a material showing a high degree of chemical specificity. In the absence of knowledge which would allow for the breakdown of protoplasm into its individual components *Ehrlich* was forced to formulate a theory according to which various definite receptor sites in this giant protoplasm molecule were specifically adapted to fit certain chemical structures. That this was something very different from the ideas then current on the colloidal adsorption of dyes is clear from the following quotation "We may regard the cell quite apart from its familiar morphological aspects, and contemplate its constitution from the purely chemical standpoint. We are obliged to adopt the view that the protoplasm is equipped with certain atomic groups (side chains), whose function especially consists in fixing to themselves certain food-stuffs of importance to cell life ... and which possess a certain degree of independence, and which may differ from one another according to the requirements of different cells".

Developing this idea further *Ehrlich* suggested that drugs which were toxic to cells were fixed by the side chain receptors because of their chemical similarity to the food stuffs which the side chains were designed to capture. The importance of these ideas on the protoplasmic side chains and on the chemical specificity of receptors cannot be over-emphasized. The thread of this idea runs through the whole of *Ehrlich*'s later work and gives it a unity which is otherwise not apparent. In addition it was the seed upon which the ideas of his successors were able to crystallize.

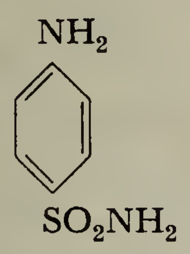
Development of the Receptor Theory

The receptor theory had its origin, as already indicated, in the observation that different cells had different reductive capacity as measured by their ability to reduce dyes of different redox potential. *Ehrlich* realized that this could explain the controlled transfer of oxygen from hæmoglobin to tissues and that oxygen was required to oxidize the nutrients also bound by the cells, so providing energy. Here is the genesis of the idea later taken up by *Rubner*, by *Warburg*, by *Keilin* and by *Wieland* and developed eventually into the study of the oxidative pathways of cell metabolism.

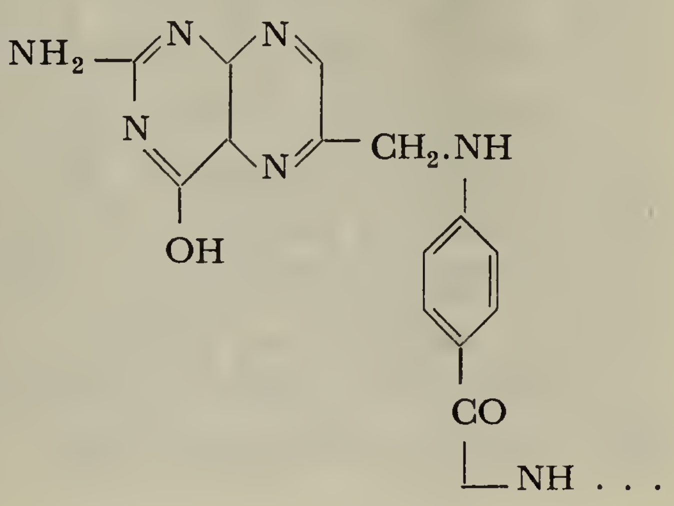
The second idea contained in the "Sauerstoffbedürfnis" was that drugs are fixed to receptors because they are chemically similar to the foodstuffs normally fixed by the receptors. This idea was taken up in 1914 by *Simon* and *Wood* who suggested that *Ehrlich*'s receptors, the nutriceptors, might be enzymes but the idea only came into full flower with the work of *Fildes* and of *Woods* in 1940. In that year *Woods* showed that the toxicity of sulphanilamide for certain bacteria could be reversed by p-aminobenzoic acid. He suggested that sulphanilamide was toxic because it resembled in chemical structure a normal cell nutrient and that it displaced this nutrient from a "receptor" in the cell. It has been shown since 1940 that p-aminobenzoic acid is an essential metabolite for many micro-organisms but that animal cells require instead pteroylglutamic acid, a more complex derivative of p-aminobenzoic acid, and presumably have no receptor of p-aminobenzoic acid to which sulphanilamide can become attached. Thus it appears that sulphanilamide is selectively toxic to micro-organisms because it attaches itself to a receptor peculiar to the micro-organism and absent from the tissues of higher animals. *Ehrlich* in a lecture given in 1913 says "I have explained above that the parasites possess a whole series of chemo-receptors which are specifically different from one another. Now if we can succeed in discovering among them a grouping which has no analogue in the organs of the body, then we should have the possibility of constructing an ideal remedy.".



p-aminobenzoic acid



sulphanilamide



pteroylglutamic acid

Antimalarials

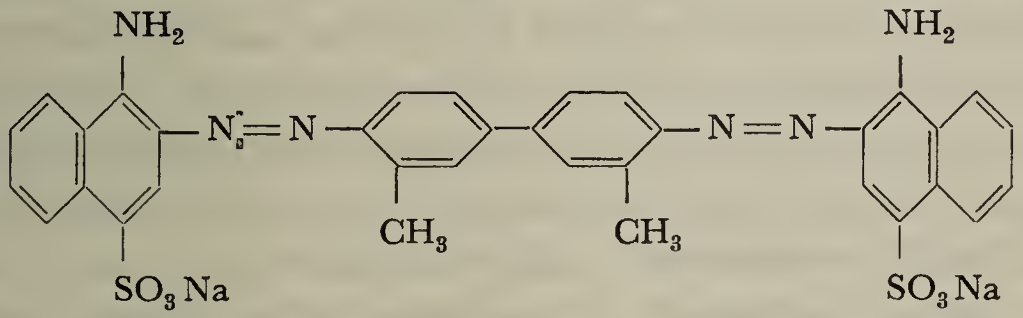
In following up his studies on the selective distribution of methylene blue in living tissues *Ehrlich* noticed that the dye was selectively adsorbed by the malaria parasite. This induced him in collaboration with *Guttmann* to try the dye on some cases of human malaria. Although the drug showed quite substantial antimalarial activity it was not as effective as quinine. Methylene blue continued to be used for many years in patients hypersensitive to quinine but its real value was in the lead it provided to the design of improved antimalarials. Anyone with practical experience in the synthesis of chemotherapeutically effective drugs soon becomes painfully aware that without some "lead", some structure which is known to be active and which can be altered and improved by structural modification, the search for new drugs is both slow and heartbreakingly full of negative results. Until the very recent accumulation of knowledge on intermediary metabolism these "leads" had as their basis *Ehrlich*'s fundamental observations on the parasitotropism of certain dyes. From the lead provided by methylene blue the research laboratories of I. G. Farbenindustrie produced plasmoquine (1924) and atebrin (1933) and these drugs in their turn guided the development of sontoquin and of its many analogues (1940–1945). Thus the pedigree of many antimalarials in use today can be traced back to *Paul Ehrlich*. The only exceptions are those based on the pyrimidine ring such as paludrine and daraprim which have as their origin the idea of building toxic analogues of essential metabolites of the pyrimidine series.

As already mentioned, *Ehrlich*'s work is divided into three periods; the first was concerned mainly with staining reactions, vital stains and cell metabolism, the second with antitoxins and the third with chemotherapy. There is however a close connexion between the first and third periods, not only because methylene blue, the first synthetic antimalarial, belongs to *Ehrlich*'s first period (1891) but also because as soon as *Ehrlich* was able to obtain the facilities and assistance required for chemical syntheses (1903) he turned back to the dyes as a natural starting point for systematic studies in chemotherapy.

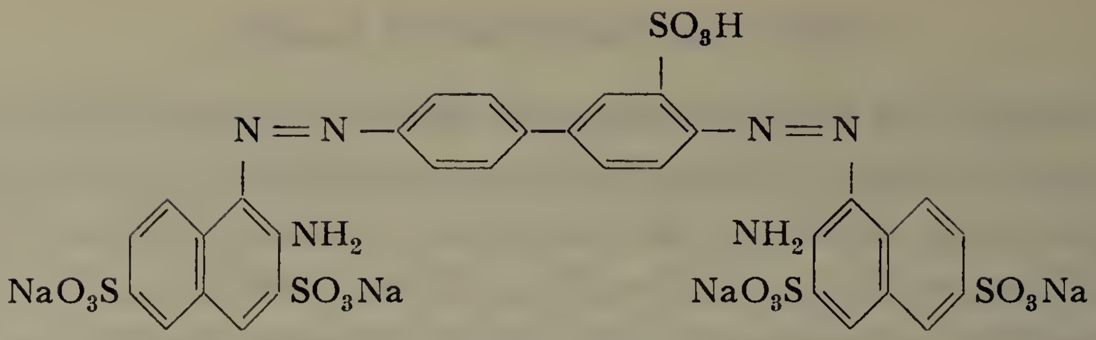
Collaboration wih Chemical Industry

The move to Frankfurt brought *Ehrlich* into close contact with the firm of Casella (later to become a subsiduary of I.G. Farbenindustrie) and with his old friend *von Weinberg*, director of the Casella factory. The cordial relations thus established with the German chemical industry including also at a later date the dye works of Meister, Lucius and Bruening at Hoechst a. Main were of great importance to the progress of chemotherapy. During his own lifetime this association enabled *Ehrlich* to call upon the services of industrial chemists for the synthesis of various chemotherapeutic drugs and after his death the tradition of chemotherapeutic research thus established was carried on in industrial laboratories and in this way many "leads" provided by *Ehrlich*'s genius bore a rich harvest.

The development of the antimalarials plasmoquine, atebrin and sontoquin starting from methylene blue has already been mentioned; another important "lead" was provided by *Ehrlich*'s studies on benzopurpurin: "I had often noticed," he says, "that benzopurpurins remain a long time in the organism and I hoped that this series would be able to do something particular. Then when I came to study trypanosomiasis, benzopurpurin was among the first substances to be tried out. It showed in the experiment little, though definite, influence and I had the idea that this weak effect must be caused by its somewhat difficult solubility. Therefore, I asked *Dr. Arthur von Weinberg* to have it made more easily soluble by introducing the solubilizing action of sulphonic acid groups." The result was the production of trypan red which was shown by *Ehrlich* and *Shiga* in 1904 to be effective in the treatment of infections due to *Trypanosoma equinum.* Two years later *Mesnil* and *Nicolle* followed

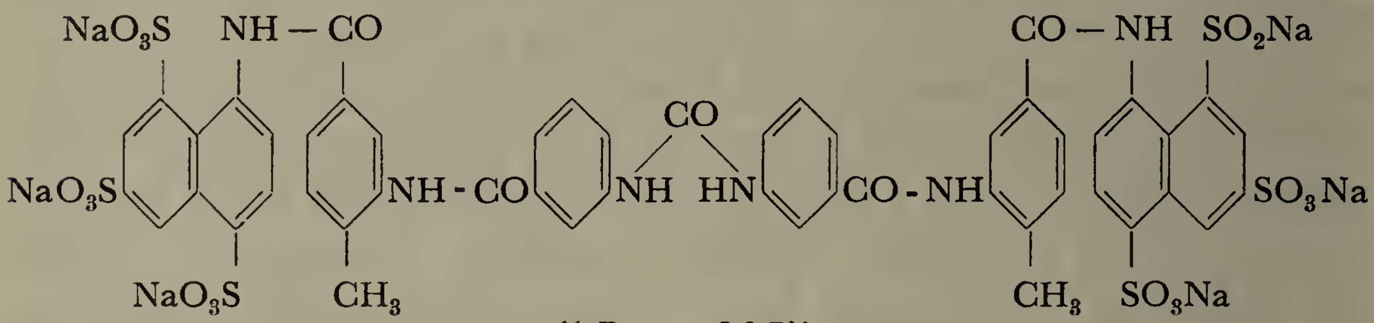


Benzopurpurin 4 B



Trypan Red

this lead and showed that trypan blue was also trypanocidal and active against *T. equiperdum* and *T. brucei.* The problem was then taken up by the commercial firm of Bayer and various methods were tried of reducing the objectionable chromogenic properties while retaining the trypanocidal action. By replacement of the azo linkages by amide links the colour was eliminated and in 1920 the company produced "Bayer 205" an excellent trypanocide active against human sleeping sickness. The derivation from *Ehrlich*'s original trypan red is obvious from the structural formula



"Bayer 205"

In looking for other trypanocidal structures *Ehrlich* tested various triphenylmethane dyes and found that though some of them showed activity they were very toxic to animals. Once again he asked for help from the Casella Chemical Company and suggested that they should prepare less basic derivatives of fuchsin. *Dr. Ludwig Benda* of Casella synthesized various analogues and one of these was found to show considerably enhanced activity. However when the preparation was repeated and a purer product obtained the activity was less. Closer examination showed that the activity was due to an impurity in the original preparation. This impurity was tracked down and shown to be acriflavine. As a trypanocide it was disappointing but as shown by *Ehrlich*'s pupil *Carl Browning* it is an excellent antiseptic and is still used widely for this purpose.

Drug Resistance

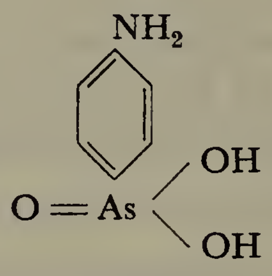
It was during the investigation of triphenylmethane dyes also that *Ehrlich* and his colleagues discovered drug resistant strains of trypanosomes. *Franke* and *Roehl* in the Frankfurt laboratory found that feeding parafuchsin to mice infected with *Trypanosoma brucei* caused disappearance of trypanosomes from the peripheral blood, but, after a week or two, relapse occurred and the parasites reappeared. Administration of the drug caused them to disappear again. This process could be repeated at further relapses but not indefinitely. After each successive administration, the time of banishment of trypanosomes from the blood became shorter, until finally the drug failed to have any effect on the parasites. This increased resistance to the drug was maintained consistently through numerous animal passages.

Later work by *Ehrlich* showed that trypanosomes could acquire resistance to all the known trypanocides such as trypan red, acriflavine and the arsenicals. He was quick to realize the practical importance of the observation. In his Harben Lectures of 1907 he says "We possess in this specific resistance a therapeutic sieve with which we can undertake the classification of any new chemotherapeutic substance". The value of this suggestion has been amply demonstrated during the past ten years in distinguishing between or identifying the many antibiotics obtained from bacterial and mould cultures. The danger of obtaining strains of pathogens permanently resistant to the available drugs was also emphasized, and in order to combat this *Ehrlich* suggested firstly that the main chemotherapeutic attack on the organism should be as complete as possible and secondly that two drugs of quite different type should be used together so as to reduce the probability of development of resistant strains. Both these suggestions tended to be ignored at first but both were eventually adopted, the latter mainly during the past five years in a successful effort to reduce the occurence of streptomycin-resistant tuberculosis. It seems likely from recent results that both p-aminosalicylic acid and *iso*nicotinic acid hydrazide are valuable as adjuvants to streptomycin mainly because they discourage the development of drug resistance.

Arsenical Drugs

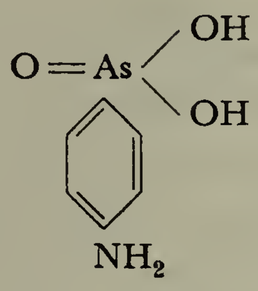
In 1906 the facilities at *Ehrlich*'s disposal were considerably augmented by the opening of the Georg Speyer-Haus, the expansion being made possible by the generosity of Frau Franzisca Speyer. The new institute was designed specifically for chemotherapeutic research.

In the same year *Thomas* and *Breinl* in Liverpool reported that the arsenical drug atoxyl had a curative action on experimental trypanosomiasis. Atoxyl had been prepared forty years previously by *Béchamp* and had been "identified" as the anilide of arsenic acid. It had also been tried in human sleeping sickness by *Koch* but although fairly effective it was highly toxic and had caused blindness in patients. With *Thomas*'s animal test available, *Ehrlich* took up the study of atoxyl. A few months later he published, in collaboration with *Bertheim*, a short paper on the structure of atoxyl in which he showed that *Béchamp*'s "identification" was mistaken and that atoxyl was in fact p-aminophenylarsonic acid. The significance of this structure was at once realized. It opened up the possibility of preparation of a whole series of analogues with substituents either on the aromatic amino group or in the benzene ring. An interesting account of the personal side of this discovery, showing *Ehrlich*'s flair for organic chemistry, has been given by Miss *Martha Marquardt* (1949) in her excellent biography of *Ehrlich*.

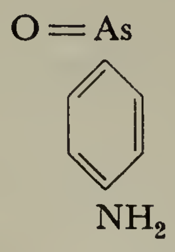


Atoxyl

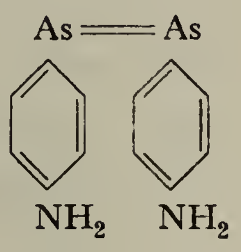
In 1903, two years before the paper by *Thomas* and *Breinl*, *Ehrlich* had tested atoxyl against trypanosomes *in vitro* but the drug had seemed inactive. In searching for the reason for the failure of these earlier tests *Ehrlich* now showed that atoxyl could be reduced to p-aminophenylarsenoxide and that this compound and its derivative p-aminophenylarsenobenzene had a strong trypanocidal action *in vitro*. Remembering his studies of 1885 on the reduction of dyes by tissues, *Ehrlich* suggested that the pentavalent arsenic of atoxyl was reduced by contact with animal tissues and that the trivalent form was the true trypanocide. Therapeutic tests showed that arsenobenzenes were rather less toxic to animals than arsenoxides and further research was concentrated on these compounds. The speed at which the investigation was carried through to a successful conclusion is astonishing even today. The structure of atoxyl was published in 1907. The improved therapeutic properties of the arsenobenzene form were recorded in 1909 and therapeutic success in the treatment of human syphilis with salvarsan was announced publicly on 17 April 1910; this despite a delay of over one year occasioned by an initial failure to detect the activity of salvarsan in animal experiments.



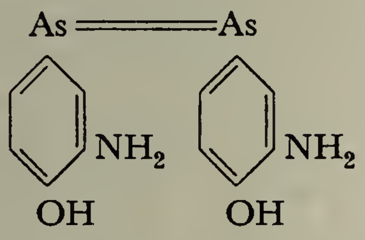
Atoxyl



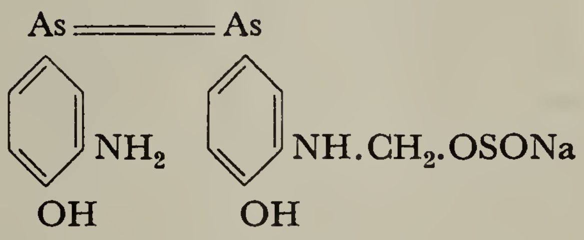
p-Aminophenylarsenoxyde



Diaminoarsenobenzene

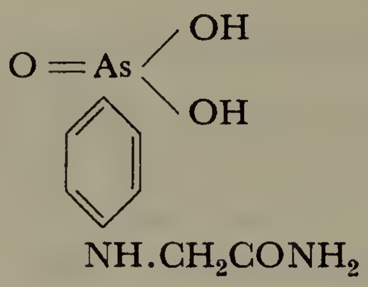


Salvarsan

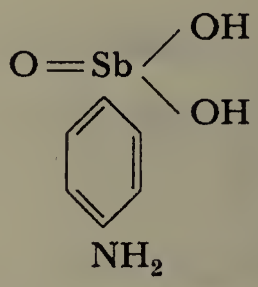


Neosalvarsan

The therapeutic success of salvarsan and of its successor neosalvarsan is too well known to require emphasis here. What was perhaps even more important was the impetus which the discovery gave to chemotherapeutic research. I have already mentioned plasmoquine, atebrin and the various chloroquinolines as the direct outcome of *Ehrlich*'s researches on malaria and Bayer 205 as the development of his discoveries in trypanosomiasis. Tryparsamide, still one of the most effective drugs in the latter stages of sleeping sickness, synthesized by *Jacobs* and *Heidelberger* in 1919, has an obvious family relationship to *Ehrlich*'s arsenicals, while the stibamines used in the treatment of leishmanial infections are derivatives of the antimony analogue of atoxyl.



Tryparsamide



Stibamine

The Treatment of Bacterial Infection—Antibody Formation

Ehrlich's preoccupation with the chemotherapy of protozoal and spirochætal infections had behind it the knowledge that many bacterial infections could be prevented or treated by immunological methods, but that these methods failed when applied to protozoal and spirochætal infections.

In discussing *Ehrlich*'s contributions to chemotherapy I have skipped from 1891 to 1904. I must now return to this period. It will be remembered that in 1891 *Ehrlich* assisted *Behring* in the development of antitoxic sera for the treatment of diphtheria and that during the following five years he worked out the standard methods of assay of toxins and antitoxins still used today. His interest in toxins had developed two years earlier in a study of immunity towards the vegetable poisons ricin, abrin and robin. He found that he could immunize lactating animals against these toxins, that the antitoxin appeared in the blood, could be passed into the milk and served to immunize the offspring. He also introduced quantitative methods into immunology and distinguished between passive and active immunity.

During this period *Ehrlich* applied all his chemical and biological knowledge to the problem of the nature of antibody and the significance of antibody formation.

In his own laboratory he had discovered three important facts; firstly, all those toxins which stimulated antitoxin production were complex molecules of large and unknown molecular weight whereas low molecular weight toxins such as the plant alkaloids did not stimulate antitoxin formation; secondly, injection of suitable toxin caused the formation of much more antitoxin than was sufficient to neutralize the toxin; thirdly, combination between toxin and antitoxin was highly specific. These were the observed facts; in order to develop a working hypothesis *Ehrlich* integrated them with existing beliefs some of which were not entirely factual. He was well aware of the deficiency of knowledge but he was a firm believer in the value of hypotheses as an aid to research. He says "the study of toxin and antitoxin is of too great practical importance for us to wait idly for years or decades until chemistry is sufficiently advanced. We must content ourselves with the slight means at our disposal". *Ehrlich*'s judgement of the situation has been amply justified with the passage of time. Not only did his *side chain theory* stimulate a vast amount of productive research, it also provided and still provides the essential basis of all subsequent ideas on antibody production. An interesting account of the growth of his ideas during this period is available in a series of private letters from *Ehrlich* to his cousin *Carl Weigert* (published in the Klinische Wochenschrift by *Heymann* in 1928).

What then was this second side chain receptor theory? The genesis of the idea goes back once more to 1885 to the "Sauerstoff-bedürfnis des Organismus". During these early investigations *Ehrlich* had convinced himself that there were present in cells certain receptors with the office of attaching foodstuffs to themselves. He says: "The relationship of the corresponding groups i.e. those of the food stuff and those of the cell must be specific. They must be adapted to one another as e.g. male and female screw or as lock and key. From this point of view we must contemplate the relation of the toxine to the cell" ... "We now come to the important question of the significance of the toxophile groups in the organs. That these are in function specially designed to seize on toxines cannot be for one moment entertained. It would not be reasonable to suppose that there were present in the organism many hundreds of atomic groups designed to unite with toxines when the latter appeared but in function playing no part in the processes of normal life, and only arbitrarily brought into relation with them by the will of the investigator. It would indeed be highly superfluous, for example, for all our native animals to possess in their tissues atomic groups deliberately adapted to unite with abrin, ricin and crotin, substances coming from the far distant tropics. One may therefore rightly assume that these toxophile protoplasmic groups in reality serve normal functions in the animal organism" (i.e. metabolism). "I think myself warranted in concluding that the formation of antitoxins lacks all the characters of the purposeful, intelligently directed and remarkable process which it at first seemed to be, and that it is to be regarded merely as a process analogous to those constituting an essential portion of the normal metabolism of the organism."

In assessing the further development of this idea by *Ehrlich* it is essential to remember that there was available to him no knowledge of the great number of proteins existing in the living organism and that the contemporary concept was, as already mentioned, of a vast complex living molecule, *protoplasm*, to which various rather less complex side chains were attached. Although the side chains were envisaged as having definite chemical affinities they were recognized as being of comparable complexity to the "albuminoid bodies" of blood. Thus in tackling the problem of antibody formation *Ehrlich* was vaguely aware, though he did not express it in such terms, that he was dealing with the problem of artificial stimulation of synthesis of specific proteins. It is hardly suprising that he failed to offer an entirely satisfying explanation of the process; we are in no position to do so even today.

Ehrlich's ideas can be best expressed in his own words "In keeping with what has already been said, the first stage in the toxic action must be regarded as being the union of the toxine by means of its haptophore group with certain side chains of the cell protoplasm. This union is, as animal experiments with a great number of toxines show, a firm and enduring one. The side chain involved, so long as the union lasts, cannot exercise its normal physiological function ... We are therefore now concerned with a defect which, according to the principles so ably worked out by Professor Carl Weigert, is repaired by regeneration. ... If after union has taken place, new quantities of toxine are administered at suitable intervals and in suitable quantities, the side chains which have been reproduced by the regenerative process are taken up anew into union with the toxine, and so again the process of regeneration gives rise to the formation of fresh side chains. In the course of the progress of typical systematic immunization ... the cells become, so to say, educated or trained to reproduce the necessary side chains in ever increasing quantity . . . Thus the lasting and ever increasing regeneration must finally reach a stage at which such an excess of side chains is produced that, to use a trivial expression, the side chains are present in too great a quantity for the cell to carry and are handed over as needless ballast to the blood."

It is instructive to compare this with the ideas of *Burnet* and *Fenner* given in their recent (1949) monograph on "The Production of Antibodies"; the language is different, the ancillary knowledge is greater, but the fundamental problem is still the same and the answer suggested by *Burnet* and *Fenner* is essentially an elaboration of the idea of *Ehrlich.* They summarize their views as follows: "There is a physiological mechanism mediated by cells of the reticuloendothelial system, plus in all probability a variety of other relatively undifferentiated mesenchymal cells including lymphocytes and plasma cells, concerned with the breaking down and disposal both of effete or damaged body cells and of foreign . . . material. Autologous material is dealt with by appropriate enzymic system without involving change from the existent status. Foreign organic material is dealt with by the same cells and processes but at some point in the mechanism a modification is necessary to allow what, for example, was effective in dealing with blood group polysaccharide, to deal with a bacterial polysaccharide. An appropriate adaptive enzyme is produced which has the necessary configuration for effective adsorption to the unfamiliar substrate . . . The essence of our hypothesis is that, irrespective of whether it is legitimate or not to call it an adaptive enzyme, a new self-replicating system is now present in the cell which can be caused to multiply by the appropriate stimulus. . . . It seems highly probable that the function of first antigenic contact is to produce the adaptive modification while subsequent contacts stimulate its replication and eventual liberation of partial replicas into the blood stream."

Interaction of Personality and Work

I have touched very lightly upon certain aspects of *Paul Ehrlich*'s work, since others better qualified than myself have covered them in separate articles in this volume. I have tried, rather, to present an overall picture of the period and to indicate some of the fruitful lines of thought initiated by *Ehrlich* and followed up by others. It is impossible to read *Ehrlich*'s original papers and articles without gaining a considerable knowledge of the personality behind the work. Some men are content to accumulate factual knowledge or to develop new methods or to organize a research school but *Paul Ehrlich* did all three with prodigous energy and with a degree of success attained by few; nevertheless his mind had the restlessness of a caged fox. He was constantly probing the limits of existing knowledge seeking for some satisfactory scaffold of theory into which he could fit his knowledge and devising new experiments to test his theories. It is a measure of the force of his personality and of the vigour of his presentation that his immunological theories, presented over a period of about five years, completely dominated immunology for the following twenty years. In these papers he expresses himself at times with a vigour which is refreshing to those accustomed to the impersonal character of contemporary scientific literature.

Ehrlich's popular reputation is based on two great practical contributions to medicine, the standardization of antitoxins and the development of drugs for the treatment of syphilis. With his generous sympathy for the sick and the weak, and his keen sense of public duty *Ehrlich* undoubtedly derived great satisfaction from these two achievements, but from reading his papers it is clear that these were the by-products of intellectual adventures rather than ends in themselves. He, himself, valued perhaps above all else the introduction of exact chemical methods and ideas into medicine and it is a measure of his vision that today chemistry, biochemistry and biophysics are fast becoming the basis of medical research; moreover *Ehrlich*'s "chemiotherapy" has now provided so many remedies that most of us die of old age.

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